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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/514,513	02/28/2000	Joseph Chappell	07678/011003	8901

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EXAMINER	
KALLIS, RUSSELL	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 02/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/514,513	CHAPPELL ET AL.	
	Examiner	Art Unit	
	Russell Kallis	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/31/2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *3 and 12* is/are allowed.

6)☒ Claim(s) *1,2,4-11 and 13-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 30 and 31 are new. Claims 1-31 are pending and examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 1-2, 4-11, 13-29 remain and new Claims 30-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for the reasons of record set forth in the Official actions mailed 7/30/2003, 3/04/2004, 6/16/2004 and 2/10/2005. Applicant's arguments filed 8/24/2004, 11/15/2004, and 3/31/2005 have been considered but are not deemed persuasive.

Applicant asserts that the results recited in the specification are consistent with the claimed enzymatic activity of the invention; that there is no basis for the argument that the disclosure is insufficient in providing an adequate written description of relevant identifying features and that one skilled in the art would recognize the invention, and thus the Applicants's are in compliance with the written description requirement (response page 12-14).

The claimed genus encompasses undisclosed or yet to be discovered sequences as well as the chimeras presented in Applicant's specification that synthesize a reaction product not produced by the non-chimeric isoprenoid synthase which broadly reads upon a totally new type of isoprenoid reaction product never produced before. Applicant only describes chimeras that

produce reaction products that have been produced before by the wild type enzymes but occur at different relative ratios of the total product formed. Applicant has only described chimeric isoprenoid synthases CH4 and CH10-CH14 that synthesized 5-epi-aristolochene and vetispiradene in varying ratios when transformed into E. coli on page 17 in Table 1, wherein 5-epi-aristolochene and vetispiradene are the natural products of the respective wild type tobacoo and hanbane enzymes domains of which are comprised within the chimera. Applicant has not described chimeras of isoprenoid synthases that synthesize novel isoprenoids or isoprenoid reaction products not produced by the wild type isoprenoid synthases.

Applicant asserts that U.S. Patent 5,824,774 resulted in novel enzymes capable of synthesizing new reaction products (response page 15). Clearly, this is speculative and the issued patent contains no chimeric isoprenoid synthases that created any novel isoprenoids whatsoever. Moreover, there is no correlation between the structure of described chimeras of U.S Patent 5,824,774 and the instant application and the function of a chimer isoprenoid synthase that producesan isoprenoid reaction product not produced by the wild type isoprenoid synthases.

Applicant further asserts that the published work of Schalk *et al.*, PNAS, 97; (22): pp. 11948-11953 shows that the authors identified the conserved domains and were able to reorganize the conserved domains to produce novel chimeric isoprenoid synthases having altered activities (response page 16). This is not made evident by Schalk *et al.* (PNAS, 97; (22): pp. 11948-11953), where the author's remarks are directed towards the involvement of specific residues and the importance of progressively placed directed mutations into a conserved region and not asymmetrically positioned domains as being determinant for changes in product formation. Further, the swapping of portions of the two respective enzymes analyzed by Schalk

et al. did not follow recognized intron exon boundaries but rather were determined as a matter of conveniently located restriction sites within the cDNA. Moreover, the publication date of the cited reference is well after the date of the priority claim (4/12/1996) of the instant application and does not support Applicant's assertion that the reference provides a description of the broadly claimed genus of chimeric isoprenoid synthase polypeptides and polynucleotides encoding said polypeptides, and thus it is not evident that there is support for chimeric isoprenoid synthases that produce novel isoprenoid products or products not produced by the wild type enzymes.

Applicant asserts that the published work of Erickson H. *et al.* J. Am. Chem. Soc.; 2003 vol. 125, pp. 6886-6888; see page 6886, is not applicable to the issues of chimeras that have the isoprenoid synthase activity that forms either 5-epi-aristolochene and vetispiradene (response pages 16-17). Those remarks were made under lack of enablement and not written description.

Applicant asserts that there is no basis for limiting Applicant's to chimeric variants of TEAS and HVS or CH4 and CH10-14 (response page 18). Since, not all isoprenoid synthases share the same mechanisms, domain requirement for activity, products formed, or relative position of specific domains, and thus Applicant has not described a representative number of chimeric isoprenoid synthases.

Applicant asserts that there is no ratio determining action of a domain in a non-chimeric isoprenoid synthase because only one product is produced by such a non-chimeric synthase (response page 18). Clearly Applicant is incorrect because the specification teaches on page 14 lines 13-20 that the TEAS isoprenoid synthase produces two isoprenoid products 5-epi-

aristolochene (80%) and a bicyclic sesquiterpene (20%), and thus there does appear to be a ratio determining action independent of the chimeric constructs.

Applicant asserts that there is no requirement in the claims for the generation of chimeras of isoprenoid synthases that synthesize novel isoprenoids (response page 18). Clearly the breadth of the claim language does encompass those novel isoprenoids i.e. "an isoprenoid product not produced". Moreover, Applicant's line of argument is contrary to arguments presented on page 15 lines 1-3 of the response that "the work of the Applicant establishes that chimeric isoprenoid synthases that catalyze a spectrum of reaction products not obtained with naturally occurring wild type isoprenoid synthases can be obtained"; and further down in the 3rd paragraph on page 15 of the response where Applicant references U.S Patent 5,824,774.

Applicant has not described chimeric isoprenoid synthases that synthesize a broad range of isoprenoid products or a broad range of specific isoprenoid products. Applicant only describes chimeric isoprenoid synthases CH4 and CH10-CH14 that produced sesquiterpenes 5-epi-aristolochene and vetispiradiene.

Claims 1-2, 4-11, 13-29 remain and new Claims 30-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for plant cells and plants comprising chimeric variants of sesquiterpene cyclases (e.g. TEAS and HVS and CH4, CH10-CH14), does not reasonably provide enablement for plant cells and plants comprising any chimeric isoprenoid synthase having an asymmetrically positioned homologous domain that synthesizes a reaction product not produced by the non-chimeric isoprenoid synthase or at least two reaction products not normally produced together by the wild type or non-chimeric isoprenoid synthase. The specification does not enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make the invention commensurate in scope with these claims. This rejection is maintained for the reasons of record set forth in the Official actions mailed 7/30/2003, 3/04/2004, 6/16/2004 and 2/10/2005. Applicant's arguments filed 8/24/2004, 11/15/2004, and 3/31/2005 have been considered but are not deemed persuasive.

Applicant asserts that the published work of Schalk *et al.*, PNAS, 97; (22): pp. 11948-11953 and Tamer *et al.* Tamer *et al.* (Arch. Biochem. and Biophys., 411 (2003) pp. 196-203; show that the authors identified the conserved domains and were able to reorganize the conserved domains to produce novel chimeric isoprenoid synthases having altered activities (response page 19). This is not made evident by Schalk *et al.* (PNAS, 97; (22): pp. 11948-11953), where the author's remarks are directed towards the involvement of specific residues and the importance of progressively placed directed mutations into a conserved region and not asymmetrically positioned domains as being determinant for changes in product formation. Further, the swapping of portions of the two respective enzymes analyzed by Schalk *et al.* did not follow recognized intron exon boundaries, as in the instant application, but rather were determined as a matter of conveniently located restriction sites within the cDNA. Furthermore, Tamer states on page 203 column 1 the last sentence of the artivle. Moreover, since the publication dates of the cited references 2000 and 2003 for El Tamer are well after the date of the priority claim (4/12/1996) of the instant application the references show that the state of the art did not and still does not support Applicant's broad claim to chimeric isoprenoid synthases that produce isoprenoid reaction products not produced in the wild type (i.e. novel isoprenoid reaction products); and do not support Applicant's assertions that the references provide enablement by reflecting the state of the art for making and using the broadly claimed genus of

chimeric isoprenoid synthase polypeptides or provide evidence that the degree of unpredictability is overcome by one of ordinary skill.

Applicant asserts that the Office has not met the burden of countering the actual examples in the specification (response page 20). Those specific examples are not rejected. Rather the lack of examples is what forms the basis of the rejection and that there is no teaching in the art or applicant's specification to support the broadly claimed genus.

Applicant asserts that reasoned statements are required and that the Schalk and El Tamer articles do not provide as such (response pages 20-21). See arguments supra.

Applicant asserts that the experimentation must be undue (response page 21); that a reasonable correlation between the teachings of the specification and the scope of the claims; and not everything necessary to practice the invention need be disclosed (response page 22); that those limitations not included in the teachings of the specification are presumed to be within the level of ordinary skill in the art and that the level of experimentation is routine (response pages 23-26).

Since there are no working examples in the specification or in the art that would provide any guidance for making chimeric isoprenoid synthases that produce novel isoprenoids the experimentation would require undue experimentation for one of skill in the art and the scope of the claims is not reasonably correlated with the teachings in the specification or in the art. See *In re Fisher,* 166 USPQ 18, 24(CCPA 1970) which teaches "That paragraph (35 USC 112, first) requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment

provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved."

Applicant asserts that the Dudareva article does not apply to the instant claims because the isoprenoid synthases taught by Dudareva do not have the conserved motif DDXXD (response page 27). The claims are not limited to isoprenoid synthases that comprise the DDXXD motif but are limited to chimeric isoprenoid synthases that comprise the motif. It should be clearly apparent to Applicant that the chimeric isoprenoid synthase is constructed from more than one isoprenoid synthase and that the source of the conserved motif need not come from than one source of the elements of the chimeric polypeptide.

Given the unpredictability in the art as to which domains from which plants would tolerate chimerization; the breadth of the claims encompassing any plant cell comprising any number of enzymatic domains selected from a broad category of isoprenoid synthases; the lack of guidance in the specification or in the prior art as to which domains of the isoprenoid synthase enzyme family would best serve the invention; one would not know based upon Applicant's disclosure which embodiments would be inoperable and predictably eliminated. Thus, undue trail and error experimentation would be needed to make and clone a multitude of non-exemplified isoprenoid synthase chimeras and to test them in a myriad of non-exemplified expression systems for a multitude of non-exemplified isoprenoid products not produced by the

wild type isoprenoid synthases. Therefore, the invention is not enabled for the scope set forth in the claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Claims 3 and 12 are allowed.

Claims 1-2, 4-11, 13-15 and 16-31 are rejected.

The claims are deemed free of the prior art given the failure of the prior art to teach or reasonably suggest a chimeric isoprenoid synthase encoding polynucletidedes comprising the coding regions of the active domains and ratio forming domain of TEAS from Tobacco and HVS from henbane and plant cells and plants transformed therewith.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (571) 272-0798. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Russell Kallis Ph.D.
February 3, 2006

RUSSELL P. KALLIS, PH.D.
PATENT EXAMINER